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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/245,198	02/05/99	BROWNING J	A003

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EXAMINER	
KERR, J	
ART UNIT	**PAPER NUMBER**
1633	11

DATE MAILED: 07/14/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/245,198	Chicheportiche et al.
Examiner	**Group Art Unit**
Janet M. Kerr	1633

☒ Responsive to communication(s) filed on *May 5, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-35* is/are pending in the application.

Of the above, claim(s) *11-25, 27, and 32-35* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-10, 26, and 28-31* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Applicant's election of Group I, claims 1-10, 26, and 28-31, in Paper No. 8, filed 5/5/00, with traverse, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). For the reasons of record the requirement is still deemed proper and is therefore made FINAL.

Claims 1-35 are pending.

Claims 11-25, 27, and 32-35 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 8, filed on 5/5/00. An examination on the merits is presented below for claims 1-10, 26, and 28-31.

Priority

If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph.

Applicants have requested benefit of priority to provisional applications 60/023,541, filed on 8/7/96, 60/028,515, filed on 10/18/96, and 60/040,820, filed on 3/18/97. However, the inventors of the instant application, and the inventors of provisional applications 60/023, 541 and 60/028,515 are different, i.e., inventor Jeffrey L. Browning is not listed as an inventor in the two provisional applications. If applicants wish benefit of priority of these two provisional applications, 37 CFR 1.48(d) provides a procedure for adding the name of an inventor in a provisional application, where the name was omitted without deceptive intent. 37 CFR 1.48(d) requires that the amendment be accompanied by: (1) a petition including a statement that the inventorship error occurred without deceptive intention on the part of the omitted inventor or

inventors; and (2) the fee set forth in 37 CFR 1.17(q). The statement of lack of deceptive intent may be included in the petition and may be signed by a registered attorney or agent. A statement of lack of deceptive intent is not required from any of the original or to be added inventors. (See MPEP § 201.03, under 37 CFR 1.48(d)).

Specification

The abstract of the disclosure is objected to because the sentence is incomplete. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities: on page 8, under "Brief Description of the Drawings", the description of Figure 5 indicates SDS-PAGE of TNF, LTα, and TRELL under reducing and non-reducing conditions, however, the labels of Figure 5 indicate that the proteins are TWEAK, TNF, and LTα. Clarification of this inconsistency is requested. On page 9, lines 6-7, it is unclear what applicants intend by the phrase "and A. no further addition, B."; clarification is requested. On page 34, line 9; page 35, lines 9, 16, and 32, appear to be missing information as designated by the "_____"; on page 24, line 15, the European patent document "EP-B31,080A" is incorporated by reference, however, as there does not appear to be any such document by that number, a copy of the patent document is requested; on page 32, line 11, clarification of the phrase "with either the mouse of human TRELL' as one may..." is requested as it is unclear what a mouse of human TRELL' represents; and on page 37, the legend does not indicate what "+", "++", or "-" represent, furthermore, it is unclear if the "+" associated with colon adenocarcinoma should be in alignment with the other notations under the "TRELL Binding" column.

Appropriate correction is required.

Claim Objections

Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 5, which is dependent on claim 2, is directed to a DNA sequence which consists essentially of SEQ ID NO 1 or SEQ ID NO 3 and which has conservative substitutions, alterations or deletions. The recited substitutions, alterations or deletions in claim 5 further expands the DNA sequences recited in claim 2 rather than further limits the DNA sequences recited in claim 2. It is suggested that applicants rewrite the claim in independent form.

Claims 2-5, 7, 9, and 26 are objected to because of the following informalities: the claims contain multiple periods ".", however, only one period should appear in a claim. To overcome this objection, applicants should delete the "." from the sequence identifiers. For example, "SEQ. ID. NO. 1" should be changed to "SEQ ID NO 1". Appropriate correction is required.

Claim Rejections - 35 USC § 101 and *35 USC § 112*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 26, and 28-31 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claim 1 is directed to a DNA sequence encoding TRELL or a fragment thereof.

Claim 2 is directed to a DNA sequence encoding TRELL, said sequence consisting essentially of SEQ ID NO 1 or SEQ ID NO 3.

Claim 3 is directed to a DNA sequence consisting essentially of SEQ ID NO 1 or SEQ ID NO 3.

Claim 4 is directed to a DNA sequence that hybridizes to at least a fragment of SEQ ID NO 1 or SEQ ID NO 3.

Claim 5 is directed to SEQ ID NOS 1 or 3 having conservative substitutions, alterations or deletions.

Claims 6-8 and 10 are directed to a recombinant DNA molecule comprising a DNA sequence encoding TRELL operatively linked to an expression control sequence (claim 6), wherein the molecule comprises SEQ ID NOS 1 or 3 (claim 7), a host transformed with the recombinant DNA molecule (claim 8), and a method of producing substantially pure TRELL by culturing the transformed host of claim 8 (claim 10).

Claim 9 is directed to a DNA sequence encoding TRELL having the amino acid sequence of SEQ ID NOS 2 or 4.

Claim 26 is directed to an antisense nucleic acid against TRELL comprising a nucleic acid sequence hybridizing to at least a portion of SEQ ID NO 1 or SEQ ID NO 3.

Claim 28 is directed to a method of expressing a gene in a mammalian cell comprising introducing a gene encoding TRELL into a cell.

Claims 29-31 are directed to a method of treating a disorder related to TRELL in a mammal comprising introducing into a cell a therapeutically effective amount of a vector comprising a gene encoding TRELL.

The specification teaches a number of utilities for the claimed nucleotide sequence: 1) to identify new diagnostics and therapeutics for numerous diseases and conditions, 2) to obtain information about and manipulate the immune system and its processes, 3) to directly trigger TRELL-mediated pharmacological events which may have useful therapeutic benefit in the treatment of cancer or the manipulation of the immune system to treat immunologic diseases, 4) for anticancer and immunoregulatory applications to be used in therapies and methods directed to other diseases, 5) to express TRELL under abnormal conditions in a gene therapy setting to enhance anti-tumor immune response or directly affect the survival of a tumor, 6) to affect the survival of an organ graft by altering the local immune response, 7) for use in antisense therapy to inhibit the expression of TRELL, 8) for administering the soluble form of TRELL as a drug to mimic the natural membrane form of TRELL, 10) for use in assays for screening drug candidates which are either agonists or antagonists of the normal cellular function of TRELL or its receptor, 11) to isolate the TRELL receptor (see pages 6-8, 13, 16, 24, and 25 of the instant application).

While the specification discloses the tissue distribution of TRELL RNA, and indicates that expression of TRELL is cytotoxic in one human adenocarcinoma cell line, there is no disclosure in the specification of the function of TRELL with respect to the biological function of TRELL in tissues which express TRELL, nor is there any disclosure in the specification of diseases or conditions associated with normal or abnormal expression of TRELL. In addition, the specification does not disclose any particular agonists or antagonists of TRELL, nor how these compounds impact on immune function or other potential TRELL-related biological activities. As such, utilization of TRELL for any diagnostic or therapeutic purpose would require further research into and characterization of the biological function of TRELL under normal and abnormal physiological conditions. Thus, the therapeutic utility for TRELL in gene therapy or antisense therapy for treatment of cancer or immunoregulatory diseases or disorders would require further research. With regard to the utility of the polynucleotide for isolating the TRELL receptor, the specification clearly states that the TRELL receptor has not yet been isolated (see page 4, line 33 to page 5, line 2 and page 38, Table III of the instant application). Therefore, the

receptor obtained by using TRELL polynucleotides would require further analysis and characterization.

These recited utilities are merely hypothetical utilities for which the claimed invention might be used, once the necessary information is known. Moreover, the asserted utilities of the polynucleotides are not considered "substantial" utilities, i.e., the asserted utilities require carrying out further research to identify or reasonably confirm a "real world" context of use. For example, the polynucleotides and peptides produced by the polynucleotides require further basic research into the biological properties and functions of polynucleotides and peptides, including the mechanism of action of the peptides; the types of cancer and/or immune related disorders which would benefit from administration of TRELL sense or antisense polynucleotides, agonists or antagonists, or polypeptides, all require further research. Consequently, there is no immediate benefit to the public since the claimed invention must be further characterized to provide the information necessary for practicing these utilities. Such further characterization amounts to research on the claimed invention itself, a non-statutory utility, including use-testing, i.e., research aimed at finding a specific utility for the invention. *Brenner v. Manson*, 148 USPQ 689, 696 (US SupCt., 1966) noted that "Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing", and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.".

Claims 1-10, 26, and 28-31 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The specification discloses that TRELL is a member of the TNF family of related ligands based on homology of TRELL to other members of the family and will function in a manner similar to the other putative ligands. While the specification discloses that the polynucleotides

encoding TRELL can be used for gene therapy, antisense therapy, for isolating its receptor which would further allow characterization of the TRELL ligand, for use in diagnostic assays, or to identify agonists or antagonists which can be used in therapeutic regimens, the specification provides only limited information on the biological function of TRELL. For example, the specification only discloses that an analysis of multiple hematopoietic and non-hematopoietic cell lines demonstrates that the expression of TRELL is cytotoxic in one human adenocarcinoma line. It is apparent, from this exemplification, that the biological function of TRELL as a cytotoxic compound for all cancer cells cannot readily be predicted based on its purported structural similarity to other TNF-related ligands of the prior art. Both the prior art, and the art at the time of filing indicate that the skilled artisan could not predict the function of a member of the TNF family of related ligands based merely on its polynucleotide or polypeptide sequence. The TNF family of ligands are structurally quite diverse (see, e.g., Gruss *et al.*, Blood, Vol. 85:3378-3404, 1995) as evidenced by the differences in the molecular characteristics (see Table 1), the structural characteristics (see Table 2) and sequence relationships (see Table 3, section C) of the TNF ligand superfamily. Moreover, the functional activities of members of TNF ligand superfamily are quite variable. For example, Darnay *et al.* (Ann. Rheum Dis., 58:(Suppl. I) I2-I13, 1999) teach that TWEAK, a member of the TNF ligand superfamily, 1) has been shown to cause weak induction of apoptosis in HT29 cells when cultured with IFNγ, 2) has been shown to cause strong induction of apoptosis in MCF-7 cells, and 3) has been shown to cause induction of proliferation in a variety of normal endothelial cells and in aortic smooth muscle cells (see page I9, right column, under the section entitled "TWEAK (TNF Relatedness and Weak Inducer of Apoptosis). As an additional example of the difficulties in establishing the biological functions of members of the TNF ligand superfamily, Degli-Esposti (J. Leukocyte Biology, 65:535-542, 1999) teaches that

> "After the cloning of TRAIL, in late 1995, it was hoped that characterization of its receptor would shed some light on the biological functions of this new cytotoxic ligand with apparently selective apoptotic activities on tumors. Almost 3 years later, the identification of five receptors for TRAIL has revealed a very complex system, but the physiological functions of this ligand remain unclear."

and further teaches that

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"Although perhaps unexpected, the pleiotropic effects of TRAIL are reminiscent of those of many other members of the TNF family. Several members of the TNF family of ligands and receptors are able to transduce a cell death signal, as well as being able to mediate other activities such as cell activation, differentiation, and proliferation. The identification of multiple receptors for TRAIL is indeed reminiscent of the intricacy surrounding the dual receptors for TNF. By analogy tot he TNF system, TRAIL activities may vary depending on the engagement of different receptors. In addition, it is possible that further TRAIL ligands are yet to be characterized, adding even further complexity to this already intricate system. As for the physiological relevance of TRAIL and its receptors, much remains to be understood."

(see, e.g., page 540, left column, first paragraph under Conclusions, and right column, first and second full paragraphs).

Clearly, in view of the structural and functional diversity of the TNF ligand superfamily, and the unrecognized physiological relevance of the members of the ligand superfamily and their associated receptors, one of skill in the art would not know how to make and use the claimed polynucleotides, fragments thereof, variants thereof, and antisense sequences thereof without undue experimentation. Moreover, as the only disclosed biological function of TRELL is as a weak inducer of apoptosis in one colon adenocarcinoma cell line, the skilled artisan would not have had a high expectation of successfully using TRELL polynucleotides or peptides (obtained from culturing host cells comprising TRELL polynucleotides), in various therapeutic regimens such as gene therapy, antisense therapy, and immunoregulatory therapy without undue experimentation. Thus, the specification is non-enabling for the claimed invention.

With regard to DNA sequences obtained by hybridization to at least a fragment of SEQ ID NOS 1 or 3 (see claims 4 and 26), the specification fails to provide adequate guidance as to which hybridization conditions are required such that all of the polynucleotides embraced by the claims hybridize to at least fragments of the nucleic acids set forth in SEQ ID NOS 1 or 3. Nucleic acid hybridization assays are extremely sensitive to the conditions in which they are performed. The buffer composition, pH, temperature, length of time, salt concentrations, quality and source of template nucleic acid, are all variables which determine the reproducibility of a given hybridization experiment. Given the unpredictability of the art and the nature of hybridization experiments in

general, it would require undue experimentation for one of ordinary skill in the art to ascertain the hybridization conditions such that all of the claimed polynucleotides and fragments thereof would be capable of selectively hybridizing to the polynucleotides of SEQ ID NOS. 1-20 and fragments thereof. For example, Carrico (US Patent No. 5,200,313) discloses factors which affect hybridization reactions including:

1. The purity of the nucleic acid preparation.
2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.
3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.
4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.
5. Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30°C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.
6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.
7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.
8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.
10. Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1 X SSC for 30 minutes at 65°C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

Given the numerous variables which impact on the capability of a polynucleotide to hybridize to any other polynucleotide, and given the lack of guidance in the specification as to which hybridization conditions are required such that hybridization can occur, one of skill in the art would not have had a high expectation of successfully obtaining the claimed polynucleotides without undue experimentation. Moreover, once obtained, the specification does not provide guidance as to how to use these particular polynucleotides. It would require undue experimentation for one of skill in the art to isolate and characterize, both structurally and functionally, all of the polynucleotides embraced by the claims.

With regard to claim 28, directed to introducing and expressing a gene encoding TRELL in a mammal, and with regard to claims 29-31, directed to a method of treating a disorder related to TRELL by introducing and expressing a gene encoding TRELL in a mammal, the only intended use of the method of claim 28, as indicated in the specification, and the stated use for the methods of claims 29-31 encompass gene therapy. However, the specification is not enabling for the methods as the specification does not disclose a TRELL gene, *per se*; the biological function of TRELL is not well-established, and therefore the therapeutic effects upon administration of TRELL is unpredictable; and the state of the art of gene therapy, in general, is neither routine nor predictable. In this

regard, in the "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" (published December 7, 1995), Orkin and Motulsky indicate that clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol; that major difficulties of gene therapy include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host; that it is not always possible to extrapolate directly from animal experiments to human studies; and that while the most straight-forward application of gene therapy may be in the treatment of single-gene inherited disorders, practical difficulties need to be addressed, i.e. delivery of the appropriate gene to a specific cell type or tissue, gaining access to the relevant cell type for correction of the defect, assessing the total fraction of cells in a tissue that need to be corrected, achieving the level of expression required for correction, and regulating expression of the added gene once it is transferred into appropriate target cells (see, e.g., pages 1 and 2, points 2, 3, and 5, for example, page 5, under "Single-gene inherited disorders", and page 14, bullet paragraphs 3-6). Similarly, Verma *et al.* (Nature, 387:239-242, 1997) indicate that "In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged; problems such as lack of efficient delivery systems, lack of sustained expression, and host immune response reactions remain formidable challenges; although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is no single outcome that we can point to as a success story" (see page 239, under Abstract, and left column, paragraphs 1-2).

With regard to antisense nucleic acids, the specification discloses that the intended use of such nucleic acids is for antisense therapy, i.e., to administer oligonucleotides or their derivatives which specifically hybridize under cellular conditions with the cellular mRNA and/or DNA encoding TRELL to inhibit expression of the encoding protein by inhibiting transcription and/or translation (see page 13, line 23 through page 14, line 10 of

the instant application). However, the specification does not provide any antisense nucleic acid sequences, the hybridization conditions required to obtain appropriate antisense nucleic acid sequences having the required characteristics, nor does the specification disclose which specific antisense nucleic acid sequences can be administered such that inhibition of TRELL expression is achieved. As indicated above, given the numerous variables which impact on the capability of a polynucleotide to hybridize to any other polynucleotide, and given the lack of guidance in the specification as to which hybridization conditions are required such that hybridization can occur, one of skill in the art would not have had a high expectation of successfully obtaining the claimed polynucleotides without undue experimentation. Moreover, the state of the art at the time of filing indicates that providing antisense constructs which are capable of inhibiting expression is neither routine nor predictable. For example, Branch (TIBS, 23:45-50, 1998) addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity; [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to

establish a compound's primary pharmacological identity; [a]ntisense compounds are no exception; [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites; [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*." Agrawal (TIBTECH, Vol. 14:376-387, 1996) states the following: "[t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering in the disease process" (see page 376, left column, first paragraph); "[o]ligonucleotides must be taken up by cells in order to be effective; [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . .[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (see page 378, under "Cell culture system and target gene"); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the

oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (see page 379, left column, lines 4-7); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (see page 379, left column, first full paragraphs).

In view of the lack of guidance in the specification as to the structure of any antisense nucleic acids, the structure of the appropriate antisense nucleic acid constructs to use in a therapeutic context, and the unpredictability of antisense therapy as indicated in the art at the time of filing, it would have required undue experimentation for the skilled artisan to make and use the antisense nucleic acids as claimed.

Claims 1, 4-10, 26, and 28-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the revised interim guidelines on written description published December 21, 1999 in the Federal Register at Volume 64, Number 244, pp. 71427-71440 (also available at www.uspto.gov).

Claim 1 is directed to a DNA sequence encoding TRELL or a fragment thereof.

Claim 4 is directed to a DNA sequence that hybridizes to at least a fragment of SEQ ID NO. 1 or SEQ ID NO. 3.

Claim 5 is directed to SEQ ID NOS. 1 or 3 having conservative substitutions, alterations or deletions.

Claims 6-8 and 10 are directed to a recombinant DNA molecule comprising a DNA sequence encoding TRELL operatively linked to an expression control sequence (claim 6), wherein the molecule comprises SEQ ID NOS 1 or 3 (claim 7), a host

transformed with the recombinant DNA molecule (claim 8), and a method of producing substantially pure TRELL by culturing the transformed host of claim 8 (claim 10).

Claim 9 is directed to a DNA sequence encoding TRELL having the amino acid sequence of SEQ ID NOS 2 or 4.

Claim 26 is directed to an antisense nucleic acid against TRELL comprising a nucleic acid sequence hybridizing to at least a portion of SEQ ID NO 1 or SEQ ID NO 3.

Claim 28 is directed to a method of expressing a gene in a mammalian cell comprising introducing a gene encoding TRELL into a cell.

Claims 29-31 are directed to a method of treating a disorder related to TRELL in a mammal comprising introducing into a cell a therapeutically effective amount of a vector comprising a gene encoding TRELL.

With regard to claims 1, 4-10, and 28-31, as written, the claims encompass polynucleotides comprising non-disclosed nucleic acid sequences attached to the claimed SEQ ID NOS. When given its broadest reasonable interpretation, the claims encompasses genes containing the nucleotide sequences of SEQ ID NOS. 1 and 3, or genes encoding the protein sequences set forth in SEQ ID NOS 2 and 4. However, there is no disclosure in the specification of genomic sequences which comprise nucleic acids associated with the claimed polynucleotides.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In this case, SEQ ID NOS. 1 and 3 are the only species whose complete polynucleotide structure is disclosed. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence). Possible identifying characteristics could include size of the polynucleotide, the location to which it maps in the genome, restriction maps, biological activity of the encoded product, etc. No such

identifying characteristics are provided for polynucleotides other than those of SEQ ID NOS 1 and 3. While applicants were obviously in possession of the nucleic acid sequences as set forth in the disclosed SEQ ID NOS 1 and 3, the specification provides no information regarding sequences which are naturally attached to the claimed nucleic acid sequences, i.e., nucleic acid sequences comprising 5' regulatory regions or introns. The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of polynucleotides besides SEQ ID NOS. 1 and 3, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

Claims 1, 4, and 5 are directed to polynucleotides encoding TRELL fragment (claim 1), DNA sequences which hybridize to at least a fragment of SEQ ID NOS 1 or 3, said DNA sequence encoding a polypeptide that is at least 30% homologous with an active site of TRELL (claim 4), and TRELL polynucleotides having conservative substitutions, deletions, or alterations (claim 5). While applicants were obviously in possession of the nucleic acid sequences as set forth in the disclosed SEQ ID NOS 1 and 3, the specification does not disclose TRELL fragments, sequences encoding an active site of TRELL and which hybridize to at least a fragment of SEQ ID NOS 1 or 3, or TRELL polynucleotides having conservative substitutions, deletions, or alterations. Given the sequence variability in the TNF family of related ligands, the skilled artisan could not envision the numerous polynucleotide structures encompassed in the claimed invention such that the polynucleotide encodes TRELL. The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of polynucleotides besides SEQ ID NOS 1 and 3, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

Claim 26 is directed to an antisense nucleic acid against TRELL comprising a nucleic acid sequence hybridizing to at least a portion of SEQ ID NOS 1 or 3. The

specification defines antisense nucleic acids in the context of antisense therapy indicating that "antisense therapy refers to administration or in situ generation of oligonucleotides or their derivatives which specifically hybridize under cellular conditions with the cellular mRNA and/or DNA encoding TRELL so as to inhibit expression of the encoded protein, i.e. by inhibition transcription and/or translation" (see page 13, lines 23-32 of the instant application). As the skilled artisan would not know, *a priori*, the sequences of oligonucleotides or derivatives thereof which have the required activity, i.e., hybridization under cellular conditions with the cellular mRNA and/or DNA encoding TRELL so as to inhibit expression of the encoded protein, nor could the skilled artisan envision the sequence of such oligonucleotides or derivatives thereof, and further in view of the lack of any examples in the specification of any oligonucleotides or derivatives thereof having the required inhibitory activity, the limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the claim designated antisense nucleic acids at the time the application was filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 26, and 28-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite because it is unclear which sequence encoding TRELL and which fragment thereof is intended, i.e., is the sequence that of SEQ ID NO 1 or 3 or an undisclosed TRELL DNA sequence? With regard to the TRELL fragment, it is unclear from which sequence the fragment was obtained, the length of the fragment, or the sequence of the

fragment. The metes and bounds of the DNA sequence encoding TRELL or a fragment thereof are unclear.

Claim 4 is rendered vague and indefinite by the phrase "an active site of TRELL" as neither the claim nor the specification defines a TRELL active site. Thus, the particular sequence that hybridizes to a DNA sequence that is at least 30% homologous with an active site of TRELL which applicants intend as the invention is unclear. It is also unclear what hybridization conditions are necessary such that the claimed DNA sequence hybridizes to at least a fragment of SEQ ID NO 1 or 3.

Claim 5 is rendered vague and indefinite by the term "A" as it is unclear if the intended DNA sequence is in fact SEQ ID NO 1 or SEQ ID NO 3, as recited in claim 2, or if the DNA sequence is distinct from the sequences recited in claim 2, which would broaden rather limit the claim upon which claim 5 depends. The term "A" should be changed to "The" to overcome this rejection. Claim 5 is further rendered confusing by the phrase "said sequence consists essentially of SEQ ID NO 1 or SEQ ID NO 3 with conservative substitutions, alterations or deletions" as it is unclear how a sequence can consist essentially of SEQ ID NOS 1 or 3 yet be different? As written, it appears that claim 5 is broadening rather further limiting claim 2. To overcome this rejection, applicants should rewrite the claim as an independent claim.

Claim 10 is rendered vague and indefinite by the phrase "producing substantially pure TRELL" as the method step only requires culturing a host cell transformed with DNA sequences encoding TRELL; as there is no purification step recited in the method, how can the method be directed to producing substantially pure TRELL? The method is missing essential steps. Claim 10 is also rendered vague and indefinite by the phrase "unicellular host" as there is no "unicellular host" recited in claim 8; the phrase lacks proper antecedent basis. The term "substantially" also renders the claim vague and indefinite as "substantially" is a relative term which is not defined in the claim or the specification. The purity of TRELL is unclear.

Claim 26 is rendered vague and indefinite by the phrase "at least a portion" because it is unclear as to the size of the portion of SEQ ID NO 1 or SEQ ID NO 3 is required such that the

antisense nucleic acid against TRELL will be capable of hybridizing. It is also unclear what hybridization conditions are necessary such that the claimed DNA sequence hybridizes to at least a fragment of SEQ ID NO 1 or 3.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 5, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Matsubara *et al.* (WO 95/14772, 6/1/95, only the front page and the page containing the appropriate sequence is provided).

Matsubara *et al.* teach a 264 base pair nucleotide sequence which has a 97.3% best local similarity to base pairs 1111 to 1373 of SEQ ID NO 3 of the instant application (see the highlighted sequence in WO 95/14772 and the highlighted sequence comparison Result 6, which was conducted on June 27, 2000 at the USPTO). As the sequence of Matsubara *et al.* is a fragment of TRELL (as required in claim 1), consists of at least 20 consecutive bases of SEQ ID NO 3 and is thus likely to hybridize to SEQ ID NO 3 barring evidence to the contrary (as required in claim 4), consists of substitutions, alterations, and deletions (as required in claim 5), and wherein the DNA sequence of Matsubara *et al.* necessarily comprises the complementary strand and will hybridize to at least a portion of SEQ ID NO 3 (as required in claim 26), the DNA sequence taught by Matsubara *et al.* anticipates the claimed invention.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However,

this application fails to comply with the requirement of 37 CFR 1.821(d) as reference must be made to the sequences disclosed on pages 27-29, 32 and 33 in the text of the description by use of the sequence identifier, preceded by "SEQ ID NO:". In addition, as Figures 1 and 2 contain sequences which have no sequence identifiers. Applicants are required to include, in the Figures, sequence identifiers for all sequences listed, or alternatively, all of the sequence identifiers can be included in the section entitled Brief Description of the Drawings.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to John LeGuyader, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-0447. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

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